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(72) Inventors JUSTUS SCHWARZ and HELLMUT JUST

(54) NEW THIOSEMICARBAZIDES

(71) We, VEB BERLIN-CHEMIE, of 125—127 Glienicker Weg, Berlin-Adlershof, Germany, a corporation organised under the laws of Eastern Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

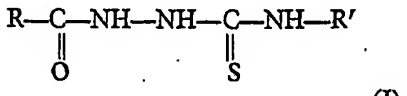
The present invention is concerned with new and virostatically-active thiosemicarbazides and with the preparation thereof and is also concerned with pharmaceutical compositions containing these new compounds.

The only virostatically-active derivative or thiosemicarbazide previously known is the thiosemicarbazide of isatin.

1 - Acyl - 4 - allyl - thiosemicarbazides have been prepared from carboxylic acid hydrazides and allyl isothiocyanate (see Gagiu *et al.*, J. prakt. Chem., 36, 108/1967) as intermediates for the synthesis of 1,3,4-thiadiazoles but a therapeutic activity of these 1-acyl-thiosemicarbazides has not been demonstrated.

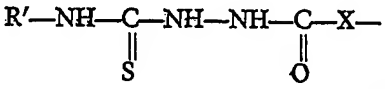
Furthermore, as tuberculostatically-active compounds, there have also been described, *inter alia*, 1 - (2 - hydroxybenzoyl) - 4 - *n* - butyl thiosemicarbazide (see M. H. Shah, J. Sci. Ind. Research, 19C, 68—70/1960) and 1 - benzoyl - 4 - naphthyl - (1) - thiosemicarbazide (see Buu-Hoi, Bull. Soc. chim. France, 1956, pp. 363—369).

According to the present invention, there is provided a new group of thiosemicarbazides which are characterised by a virostatic activity, these new compounds having the general formula: —



(I)

wherein R′ is a phenyl, 4-chlorophenyl, cyclohexyl, benzyl, naphthyl-(1), naphthyl-(2), or *n*-butyl radical and R is a 4-nitrophenyl-, styryl, adamantyl-(1), 4-chlorophenoxymethyl, phenyl or carbethoxy radical or a radical of the general formula: —

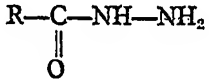


(II)

wherein R′ has the same meaning as above and X is an alkylene radical.

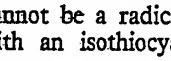
For the preparation of the new compounds (I) in which R is other than a radical of general formula (II), there can be used, for example, one of the following methods: —

a) reaction of a carboxylic acid hydrazide of the general formula: —



(III)

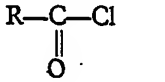
wherein R has the same meaning as above except that it cannot be a radical of general formula (II), with an isothiocyanate of the general formula: —



(IV)

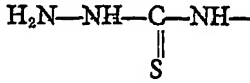
wherein R′ has the same meaning as above; or

b) reaction of a carboxylic acid chloride of the general formula: —



(V)

wherein R has the same meaning as above except that it cannot be a radical of general formula (II), with a thiosemicarbazide of the general formula: —



(VI)

[*Price 25p*]

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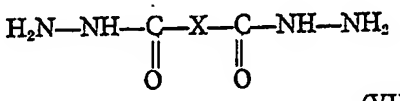
wherein R′ has the same meaning as above.

The new compounds (I) in which R is a radical of general formula (II) can be prepared, for example, by the reaction of a dicarboxylic acid hydrazide of the general formula:—



(VII)

wherein X has the same meaning as above, with an isothiocyanate of the general formula:—

(IV)

wherein R′ has the same meaning as above.

The preparation of the new compounds according to the present invention is preferably carried out in an inert solvent, such as an alcohol, for example ethanol, or in a chlorinated hydrocarbon for example chloroform. Furthermore, the preparation is preferably carried out at an elevated temperature, expediently at the reflux temperature of the reaction mixture.

The present invention also provides pharmaceutical compositions containing at least one of the new compounds of general formula (I), in admixture with a solid or liquid pharmaceutical diluent or carrier.

The following Examples are given for the purpose of illustrating the present invention:—

EXAMPLE 1.

6.6 g. (0.05 mole) oxalic acid ethyl ester monohydrazide are dissolved in the smallest possible amount of warm ethanol and 7.5 g. (0.055 mole) phenyl isothiocyanate, dissolved in the same volume of ethanol, added thereto dropwise, while stirring. After a short time, a precipitate forms. The reaction mixture is heated under reflux for 1 hour, cooled and the solid material filtered off with suction and recrystallised from ethanol. There are obtained 11.5 g. (88% of theory) 1-carbethoxycarbonyl - 4 - phenyl - thiosemicarbazide, which has a melting point of 153—154°C.

EXAMPLE 2.

10 g. (0.058 mole) 4-cyclohexyl thiosemicarbazide are dissolved in 60 ml. warm chloroform and 11.9 g. (0.064 mole) 4-nitrobenzoyl chloride, dissolved in 30 ml. chloroform, are added thereto dropwise, while stirring. The reaction mixture is then heated under reflux for a further 3 hours, a weak evolution of hydrogen chloride occurring. After cooling, the solid material is filtered off with suction and recrystallised from acetic acid. There are obtained 13 g. (40% of theory) 1 - (4 - nitrobenzoyl) - 4 - cyclohexyl-thiosemicarbazide, which as a melting point of 203°C.

The following compounds are prepared in a manner analogous to that described in the two above Examples, starting from the appropriate materials:

1 - (4 - chlorophenoxyacetyl) - 4 - phenyl - thiosemicarbazide; m.p. 192°C.; yield 91%;

1 - benzoyl - 4 - naphthyl - (2) - thio - semicarbazide; m.p. 178°C.; yield 93%;

1 - (4 - chlorophenoxyacetyl) - 4 - naphthyl - (1) - thiosemicarbazide; m.p. 170°C.; yield 95%;

1 - adamantoyl - (1) - 4 - cyclohexyl - thiosemicarbazide; m.p. 234°C.; yield 89%;

1 - cinnamoyl - 4 - *n* - butyl - thiosemicarbazide; m.p. 169°C.; yield 64%;

malonyl - bis - [4 - cyclohexyl - thio - semicarbazide-(1)]; m.p. 203°C.; m.p. 81%;

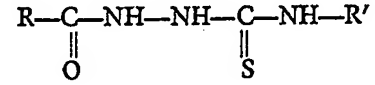
succinyl - bis - [4 - (4 - chlorophenyl) - thiosemicarbazide-(1)]; m.p. 182°C.; yield 92%;

succinyl - bis - [4 - phenyl - thiosemicarbazide-(1)]; m.p. 163°C.; yield 92%; and

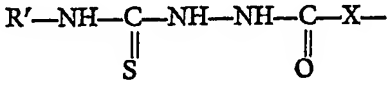
succinyl - bis - [4 - benzyl - thiosemicarbazide-(1)]; m.p. 192°C.; yield 91%.

WHAT WE CLAIM IS:—

1. Thiosemicarbazides of the general formula:—



wherein R′ is a phenyl, 4-chlorophenyl, cyclohexyl, benzyl, naphthyl-(1), naphthyl-(2) or *n*-butyl radical and R is a 4-nitrophenyl, styryl, adamantyl-(1), 4-chlorophenoxymethyl, phenyl or carbethoxy radical or a radical of the general formula:—



wherein R′ has the same meaning as above and X is an alkylene radical.

2. 1 - Carbethoxycarbonyl - 4 - phenyl - thiosemicarbazide.

3. 1 - (4 - Nitrobenzoyl) - 4 - cyclohexyl - thiosemicarbazide.

4. 1 - (4 - Chlorophenoxyacetyl) - 4 - phenyl-thiosemicarbazide.

5. 1 - Benzoyl - 4 - naphthyl - (2) - thio - semicarbazide.

6. 1 - 4 - Chlorophenoxyacetyl) - 4 - naphthyl-(1)-thiosemicarbazide.

7. 1 - Adamantoyl - (1) - 4 - cyclohexyl - thiosemicarbazide.

8. 1 - Cinnamoyl - 4 - *n* - butylthiosemi - carbazide.

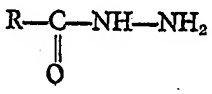
9. Malonyl - bis - [4 - cyclohexyl - thio - semicarbazide-(1)].

10 Succinyl - bis - [4 - (4 - chlorophenyl) - thiosemicarbazide-(1)].

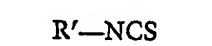
11. Succinyl - bis - [4 - phenyl - thio - semicarbazide-(1)].

12. Succinyl - bis - [4 - benzyl - thio - semicarbazide-(1)].

13. Process for the preparation of compounds of the general formula given in claim 1 in which R is other than a radical of the general formula given in claim 1, wherein a carboxylic acid hydrazide of the general formula:—

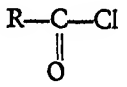


in which R has the same meaning as in claim 1 except that it cannot be a radical of the general formula given in claim 1, is reacted with an isothiocyanate of the general formula:—

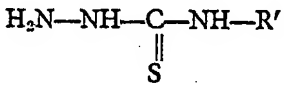


in which R′ has the same meaning as in claim 1.

14. Process for the preparation of compounds of the general formula given in claim 1 in which R is other than a radical of the general formula given in claim 1, wherein a carboxylic acid chloride of the general formula:—

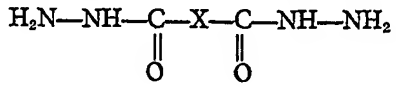


in which R has the same meaning as in claim 1 except that it cannot be a radical of the general formula given in claim 1, is reacted with a thiosemicarbazide of the general formula:—



in which R′ has the same meaning as in claim 1.

15. Process for the preparation of compounds of the general formula given in claim 1 in which R is a radical of the general formula given in claim 1, wherein a dicarboxylic acid hydrazide of the general formula:—



in which X has the same meaning as in claim 1, is reacted with an isothiocyanate of the general formula given in claim 13.

16. Process according to any of claims 13—15, wherein the reaction is carried out in an inert solvent.

17. Process according to claim 16, wherein the insert solvent is an alcohol or a chlorinated hydrocarbon.

18. Process according to any of claims 13—17, wherein the reaction is carried out at an elevated temperature.

19. Process according to claim 18, wherein the reaction is carried out at the reflux temperature of the reaction mixture.

20. Process for the preparation of compounds of the general formula given in claim 1, substantially as hereinbefore described and exemplified.

21. Compounds of the general formula given in claim 1, whenever prepared by the process according to any of claims 13—20.

22. Pharmaceutical compositions, containing at least one compound of the general formula given in claim 1, in admixture with a solid or liquid pharmaceutical diluent or carrier.

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